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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,505	02/08/2002	Ingrid Henriksen	NIDN-10439	8899

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IP DEPARTMENT
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EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
05/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/071,505	HENRIKSEN ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,11,12 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5-7, 11, 12 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Response to Arguments

Applicant's arguments filed 2/1/2007 have been fully considered but they are not persuasive. The applicants have asserted on page 2 of the remarks:

"The terms "infusion" or "continuous infusion" is not found in the specification and the claims of WO 97/48337 and also not in the specification of US patent 6,033,645. Hence, the mention of "continuous infusion" was first published on 7th March 2000 which is the publication date of the cited US patent. The instant application claims priority from 27th August 1999, GB 9920392. Applicant therefore holds that US patent 6,033,645 is not valid as 103a prior art with regard to the features related to "infusion" in the instant claims."

The examiner respectfully disagrees. First, in order to accept applicant's assertion the examiner would have to assume the issued patent, its specification and its claims are not valid, and that the examiner of the issued patent issued an invalid patent. The examiner does not see any support for such a position and hence, does not agree with the applicant's assertion. Second, the '645 patent states in col. 51 lines 21-56:

> "In accordance with the embodiment depicted in FIG. 2, the system may be utilized as described hereinafter. The needle (not shown) is inserted into an appropriate blood vessel in the patient (not shown), such as the antecubital fossa vein. The plunger 18' is depressed, causing the contrast agent 20' to be ejected from the syringe 14' into the port 44. The contrast agent 20' will generally pool or

collect in the port 44, and may also become distributed throughout the tubing 30'. Since in the present embodiment the contrast agent 20' is not ejected into the patient from the syringe 14', the rate at which the plunger 18' is depressed will generally not affect the quality of the image obtained during the subsequent diagnostic imaging.

The flush agent 24' is desirably administered after ejection of the contrast agent 20'. This generally involves operation of the control means 42' to drive the mechanical injector 22'. As with the embodiment discussed above, the control means 42' controls the amount of power supplied to the mechanical injector 22' and permits regulation of the rate at which the mechanical injector 22' operates and, thereby, the rate at which the flush agent 24' is ejected from the mechanical injector 22'. The flush agent 24' is ejected from the mechanical injector 22' and into and through the tubing 30' and the port 44. The flush agent 24' serves to push or drive the contrast agent 20 from its location in the port 44 and/or the tubing 30', throughout the length of the tubing 30', and into the patient. Preferably, the mechanical injector 22' is operated, for example, via the control means 42', to provide a flush injection rate of from about 0.05 to about 2 mL/sec. The flush may be stopped after contrast agent 20' has been administered to the patient. Alternatively, the flush may be continued so that the flush agent 24' is also injected into the patient. The rate at which the mechanical injector 22' is operated may be varied at any time during the ejection of the flush agent 24', as desired."

The '645 patent clearly indicates in this section that the flush agent can be administered after the contrast agent and then stopped or the flush may be continued so that the flush agent is also injected into the patient. This clearly indicates a "continuous infusion". Further evidence that continuous infusion is contemplated is found throughout the specification wherein the administration of the compounds and flush agents are preferably through IV administration either by injection via syringe or by injection via a mechanical injector such as a pneumatic or hydraulic injector.

The applicant's have furthered argued, on page 4 of the remarks that the prior art does not teach that at least a portion of contrast agent is mixed with the flushing agent prior to administration into the subject. The examiner points out the passage quoted above from the '645 patent that clearly shows that the flush agent does indeed mix with contrast agent prior to ejection into the patient. Indeed the flush agent pushes and/or drives the contrast agent forward and into the patient, this entails that the flush agent must interact with the contrast agent prior to ejection into the patient.

The examiner wishes to note that the '645 patent and the WO 97/48337 both claim priority to US Application 08/666129 and have identical specifications. As such, the WO document with a publication date of 24 December 1997 supports the use of the terms "continuous infusion" as claimed in the '645 patent.

The applicants have not amended the claims and the remarks/arguments are not deemed sufficient to overcome the rejections of the prior office action. As such, the rejections are maintained for the reasons stated above and for the reasons of record. The rejections are reproduced below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1,3, 5-7, 11-12, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger US Patent 6,033,645.

Unger discloses methods of administering a gaseous contrast agent comprising administering the contrast agent and a flushing agent from two different vessels into tubing that enters an upper extremity of a patient. (see figures 1-2; abstract, col 6, line

49-col 7, line 20; col 53, lines 35-67). The rates of infusion of Unger fall within the scope of the instant limitation of claim 1, "controllably," because it falls within the ranges that are described by Unger (see col 44-47). Unger claims delivery of his contrast agent in a continuous infusion (col 64, lines 20-29). The position of the syringe carrying the contrast agent in Unger is vertical (see figure 1). Unger uses the piston of the syringe as the driver (see element 18 of figure 1).

The flushing agent of Unger is normal saline (col 49, lines 53-55; col 57, line 9).

The flushing step of Unger allows complete transport of the gaseous contrast agent into the bloodstream; thus, at least a portion of the contrast agent of Unger is mixed with the flushing agent of Unger prior to administration into the subject. (col 47, lines 60-col 48, line 10). Unger further explicitly teaches flush rates that fall within the scope of the instant claim 19 (col 48, line 64-col 49, line 25).

Unger claims administration of sulfur hexafluoride and perfluorocarbon filled vesicles such as perflurobutane as his contrast agent (see examples, also col 57, lines 9-21). The vesicles of Unger include albumin-stabilized microbubbles (see col 35, line53-col 36, line 30). Thus, limitations of claims 5-7, 11-12 are also met.

Even though, Unger fails to explicitly recite the instantly claimed infusion period of 5-60 minutes, he explicitly places one of ordinary skill in the art at notice that the rate of administration can be optimized based on the volume of the composition, gaseous vesicles, type of encapsulation and other patient variable such as age, area of interest, etc... Unger makes such statements at numerous places in his patent. For example,

Unger at col 45 states:

The compositions may be administered over a period of time which can vary and depends upon a variety of factors including, for example, the volume of the composition being administered, the age and weight of the patient, the particular materials employed in the compositions, including, for example, lipids, polymers, proteins, vesicles, gases and/or gaseous precursors, the purpose for the administration (for is example, diagnostic or therapeutic), the region of interest, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. An exemplary adm/n/strati6n time for the compositions described above is about 5 seconds. Dividing the gas dose by this time period 20 provides a gas administration rate which can be expressed as cc gas/Kg-sec. Thu~ s gas dose of, for example, about $1x10^{-4}$ cc gas/Kg and an administration time of 5 sec provides a gas administration rate of about 2×10^{-5} cc gas/Kg-sec.

It is to be understood that the foregoing specific gas concentrations, composition doses, administration times and administration rates are for purposes of illustration only, and not for purposes of limitation.

Note that Unger states that any exemplified rate is for purposes of illustration not for purposes of limitation. (see col 45, lines 25-28).

At col 47 Unger explicitly states that

> As would be apparent to one skilled in the art, based on the present disclosure, the rate at which the lipid and/or vesicle compositions are preferably administered can vary, depending, for example, on the lipids, polymers, proteins, vesicles, gases and/or gaseous precursors employed, the age and the weight. of the patient, the mode of administration, the size of the vesicles (in the case of vesicle compositions), and the like. Typically, administration may be carried out at lower rates and the rate can be increased until a desired effect is achieved.

Thus, as encouraged by Unger modifying the rate of administration to observe a desired clinical effect is within the scope of the teaching of Unger. .

Subsequently, absent a showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the rate of administration of the contrast agent of Unger by routine experimentations and enhance the quality of images, because Unger explicitly recites the rate dependent factors. Thus, one of ordinary skill in the art would have had a reasonable expectation of success in achieving optimal images by determining the optimal rate of infusion.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER